PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Physiotherapy and Combined Cognitive-Behavioural Therapy for Patients with Chronic Pelvic Pain Syndrome: Results of a Non-Randomized Controlled Feasibility Trial.
AUTHORS	Brünahl, Christian A.; Klotz, Susanne; Dybowski, Christoph; Albrecht, Rebecca; Höink, Johanna; Fisch, Margit; Ketels, Gesche; Löwe, Bernd

VERSION 1 – REVIEW

REVIEWER	Zadro, Joshua University of Sydney, Institute for Musculoskeletal Health, School of Public Health
REVIEW RETURNED	09-Jun-2021

GENERAL COMMENTS	I thank for authors for the opportunity to do this statistical review. The authors aimed to explore the feasibility of a combined psychotherapeutic and physiotherapeutic treatment for patients with chronic pelvic pain syndrome. The methods mostly resembled that of a feasibility study, however some parts need to be revised to ensure the feasibility aims are consistent with the methods and how the findings are framed. 1) The authors need to make clear what aspects of feasibility they are interested in. Is it the feasibility of DELIVERING physiotherapy and combined cognitive-behavioural therapy for patients with chronic pelvic pain syndrome or the feasibility of EVALUATING this intervention in a future adequately powered RCT? If aspects of both feasibility are being assessed, the authors should make it clear which outcomes relate to DELIVERING and which relate to EVALUATING. At the moment, it just looks like the authors were interested in feasibility outcomes for EVALUATING the intervention in a larger trial, which is okay. But this needs to be clearer. 2) I would encourage the authors to take a look at this paper describing some key tips to designing and reporting a feasibility study https://pubmed.ncbi.nlm.nih.gov/23433271/ and an example of a well reported one https://bmcfampract.biomedcentral.com/articles/10.1186/s12875-019-1074-9. One key issue with the current paper is the use of statistical inference testing. Statistical inference testing should not be performed in a feasibility study because the study is likely underpowered and (in the case of this study) there was no randomisation. It would be more appropriate to describe patient outcomes between the study arms (without comparing them directly). The current statistical analysis section needs to be revised to reflect this.

	3) In addition, the conclusion and other main messages of this paper should focus on the feasibility outcomes (not between- or within-group changes in patient outcomes); feasibility outcomes should be the primary outcomes of this study and be emphasised in the conclusions. 4) Acceptability was mentioned in the aim and in several places in the paper, but I could not see how it was assessed in the study. Usually acceptability is assessed through qualitative interviews. 5) It wasn't clear how satisfaction was assessed. Qualitative data was reported in the results but there was no mention of how this data was assessed or analysed in the methods

REVIEWER	Horne, Andrew The University of Edinburgh MRC Centre for Reproductive Health
REVIEW RETURNED	16-Jul-2021

GENERAL COMMENTS	The authors of this study aimed to explore the feasibility of performing a future RCT to determine the efficacy of combining physio- and psychotherapy to treat patients with chronic pelvic pain syndrome (CPPS). Research into the management of CPPS is important because CPPS is relatively common and difficult to manage. 1. It is disappointing that the authors did not design a feasibility study that included a 'randomisation arm' as this would have provided them with a stronger indication of whether their planned future RCT was feasible. 2. I do not understand why 'satisfaction with the therapy' was included as an indication of feasibility. Surely this would come under 'acceptability' in a future RCT? It would have been better to interview participants about their experience of taking part in the study e.g. the acceptability to participants of the proposed methods of recruitment, randomisation and assessment tools. Were women happy with the content, tone, and length of the trial information received? What did they think of the questionnaires e.g. time taken to complete them, etc? 3. It is not clear how the authors determined their sample size and assignment to each group (36 and 18?). I realise that this is a feasibility study bit I still think some basic justification is required. 4. In advance of the study, it would have been helpful if the authors had set 'a willingness-to-participate rate' and 'retention rate' so they could determine whether they had achieved these feasibility outcomes (e.g. less than, or more than, expected). The primary and secondary objectives could have been outlined much more clearly. 5. Why were patients not involved in the design of the study? Surely this is important. 6. Whilst it is helpful to have reported a 'signal' of the efficacy of the intervention, I think that this information inappropriately dominates the discussion. It would be better to stress the outcome of their assessment of the processes that would be vital to the success of their future RCT. How will the results of this feasibility study shape the design of the future RCT?

	7. It would have been helpful if the authors had provided an indication of a power calculation for their proposed future RCT (based on the data from this study) in their discussion.

REVIEWER	Amer, Saad University of Nottingham School of Medicine, Division of Medical Sciences & Graduate Entry Medicine
REVIEW RETURNED	25-Jul-2021

GENERAL COMMENTS	This is small non-randomised feasibility and accessibility trial comparing combined physio- and psycho-therapy versus standard treatment in 60 patients with chronic pelvic pain syndrome (CPPS). This is an interesting pilot study, which addresses a clinically relevant and important topic. The main findings include low eligibility rate (44% of screened patients), low willingness-to-participate rate (34.8%), a satisfactory drop-out rate (27.8%) and high satisfaction amongst those receiving the intervention. The study found no significant effect of intervention on health-related QoL (measured by SF-12) and a small beneficial effect on pain (measured by Pain Disability Index (DPI)) compared to conventional treatment. The authors concluded that the combination of psycho- and physiotherapy was feasible in general; but requires some modification in future studies to improve acceptability. Overall, the trial is well conducted, and the manuscript is well written and therefore deserves consideration for publication. However, there are few issues that need attention by the authors before publication: 1. The authors stated that the control group received treatment as usual. They should provide details of this usual treatment and whether it varies between different patients. This is important so that we know wht we comparing the intervention against. 2. The authors reported results of comparison between two sequences of treatment (psychotherapy followed by physiotherapy vs physiotherapy followed by psychotherapy) in the intervention group. However, this is not mentioned under the methods section. Although it is described in the protocol, it is important to mention this under the methods section 3. As this is a pilot feasibility trial, the authors should calculate the sample size for future trials and advise on what should be the primary outcomes.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Joshua Zadro, University of Sydney

Comments to the Author:

I thank for authors for the opportunity to do this statistical review. The authors aimed to explore the feasibility of a combined psychotherapeutic and physiotherapeutic treatment for patients with chronic pelvic pain syndrome. The methods mostly resembled that of a feasibility study, however some parts

need to be revised to ensure the feasibility aims are consistent with the methods and how the findings are framed.
Answer: Thank you for reviewing our manuscript and your valuable feedback.

1) The authors need to make clear what aspects of feasibility they are interested in. Is it the feasibility of DELIVERING physiotherapy and combined cognitive-behavioural therapy for patients with chronic pelvic pain syndrome or the feasibility of EVALUATING this intervention in a future adequately powered RCT? If aspects of both feasibility are being assessed, the authors should make it clear which outcomes relate to DELIVERING and which relate to EVALUATING. At the moment, it just looks like the authors were interested in feasibility outcomes for EVALUATING the intervention in a larger trial, which is okay. But this needs to be clearer.

Answer: Thanks for the request for clarification. Our aim with this pilot study was indeed testing both the feasibility of delivery and evaluating. Thus, we have made adaptations throughout the whole manu-script including the abstract to clarify our aim and to point out how each aspect of feasibility was opera-tionalized and addressed.

2) I would encourage the authors to take a look at this paper describing some key tips to designing and reporting a feasibility study https://pubmed.ncbi.nlm.nih.gov/23433271/ and an example of a well reported one

https://bmcfampract.biomedcentral.com/articles/10.1186/s12875-019-1074-9. One key issue with the current paper is the use of statistical inference testing. Statistical inference testing should not be performed in a feasibility study because the study is likely underpowered and (in the case of this study) there was no randomisation. It would be more appropriate to describe pa-tient outcomes between the study arms (without comparing them directly). The current statistical analysis section needs to be revised to reflect this.

Answer: We agree with the reviewer on all points. We have now described these aspects in more detail in the methods section (p. 10, ll. 191-198). Since the purpose of the feasibility study was also to test the feasibility of the analyses, we have still left the inferential statistical results in Tables 1-4. However, with regard to the interpretation of these results in the methods section, we have drawn the readers' atten-tion to the insufficient power and the non-randomized design. Of course, we are happy to remove the p-values from tables x-y should the journal editor so suggest.

3) In addition, the conclusion and other main messages of this paper should focus on the feasibility outcomes (not between- or within-group changes in patient outcomes); feasibility outcomes should be the primary outcomes of this study and be emphasised in the conclusions.

Answer: Thanks for your deliberations. We have changed the discussion and conclusion section in order to sharpen the focus on the feasibility outcomes (pp. 16-21).

4) Acceptability was mentioned in the aim and in several places in the paper, but I could not see how it was assessed in the study. Usually acceptability is assessed through qualitative interviews.

Answer: Thanks for this remark. We have measured acceptance of this treatment regimen by patients with the aid of a questionnaire. To point out this operationalization we have changed the Assessments section (p. 10, ll. 184-190) and we have also deleted the word acceptability, which indeed might be con-fusing.

5) It wasn’t clear how satisfaction was assessed. Qualitative data was reported in the results but there was no mention of how this data was assessed or analysed in the methods

Answer: Thanks for this request for clarification. We have added a paragraph about the questionnaire and its content in the Assessments section (p. 10, ll. 184-190).

Reviewer: 2
Dr. Andrew Horne, The University of Edinburgh MRC Centre for Reproductive Health Comments to the Author:
The authors of this study aimed to explore the feasibility of performing a future RCT to determine the efficacy of combining physio- and psychotherapy to treat patients with chronic pelvic pain syndrome (CPPS). Research into the management of CPPS is important because CPPS is relatively common and difficult to manage.

Answer: Thank you very much for your kind feedback on our work.

1. It is disappointing that the authors did not design a feasibility study that included a 'randomi-sation arm' as this would have provided them with a stronger indication of whether their planned future RCT was feasible.

Answer: Thank you very much for this valuable comment. We are aware that this pilot study is clearly different from an RCT and that the pilot study would have benefited from randomisation. We have re-vised the manuscript to make it clear at every point that this is not an RCT. Our aim was to lay the foun-dations for an RCT with this study, while adhering to good scientific practice.

2. I do not understand why 'satisfaction with the therapy' was included as an indication of feasi-bility. Surely this would come under 'acceptability' in a future RCT? It would have been better to in-terview participants about their experience of taking part in the study e.g. the acceptability to partici-pants of the proposed methods of recruitment, randomisation and assessment tools. Were women happy with the content, tone, and length of the trial information received? What did they think of the questionnaires e.g. time taken to complete them, etc?

Answer: Thank you very much for this valuable comment. Qualitative analyses also seem very important to us, whereby a survey of both genders seems important. To our regret, this was not possible in the pilot study. However, this should urgently be taken into account in an RCT.

3. It is not clear how the authors determined their sample size and assignment to each group (36 and 18?). I realise that this is a feasibility study bit I still think some basic justification is required.

Answer: Thank you for this valuable comment. We have revised the manuscript at this point to provide more clarity. Because the participants had to come to the University Medical Centre Hamburg-Eppendorf or a longer period of time (about six months), participation in the therapy groups was not possible for many of them due to their place of residence.

4. In advance of the study, it would have been helpful if the authors had set 'a willingness-to-participate rate' and 'retention rate' so they could determine whether they had achieved these fea-sibility outcomes (e.g. less than, or more than, expected). The primary and secondary objectives could have been outlined much more clearly.

Answer: Thanks a lot for these remarks. We are of one mind with you that setting the rates in advance would have been helpful. Nevertheless, we have discussed and compared our rates with published rates. We have expanded this paragraph in the Discussion section (p. 18, ll. 357-372). Furthermore, we have adapted the study objective (p. 6, ll. 101-103).

5. Why were patients not involved in the design of the study? Surely this is important.

Answer: Thank you for this valuable comment. We agree with you, that patients should be included in the planning of a future RCT. Thus, we have included this issue in our discussion (p. 21, ll. 437-439).

6. Whilst it is helpful to have reported a 'signal' of the efficacy of the intervention, I think that this information inappropriately dominates the discussion. It would be better to stress the outcome of their assessment of the processes that would be vital to the success of their future RCT. How will the results of this feasibility study shape the design of the future RCT?

Answer: Thank you for this valuable comment. We have revised the discussion and put a clear focus on the planning of an RCT. We agree that this is very helpful for the readers of the manuscript (pp. 16-21).

7. It would have been helpful if the authors had provided an indication of a power calculation for their proposed future RCT (based on the data from this study) in their discussion.

Answer: Thank you for this comment. We have now explained in more detail that one aim of this feasi-bility study was to estimate effect sizes for power analysis for future randomized trials and why we con-sequently did not conduct our own power analysis for this feasibility study (p. 10, ll. 191-198).

Reviewer: 3

Dr. Saad Amer, University of Nottingham School of Medicine Comments to the Author:

This is small non-randomised feasibility and accessibility trial comparing combined physio- and psy-cho-therapy versus standard treatment in 60 patients with chronic pelvic pain syndrome (CPPS). This is an interesting pilot study, which addresses a clinically relevant and important topic. The main find-ings include low eligibility rate (44% of screened patients), low willingness-to-participate rate (34.8%), a satisfactory drop-out rate (27.8%) and high satisfaction amongst those receiving the intervention. The study found no significant effect of intervention on health-related QoL (measured by SF-12) and a small beneficial effect on pain (measured by Pain Disability Index (DPI)) compared to conventional treatment. The authors concluded that the combination of psycho- and physiotherapy was feasible in general; but requires some modification in future studies to improve acceptability.
Overall, the trial is well conducted, and the manuscript is well written and therefore deserves consid-eration for publication. However, there are few issues that need attention by the authors before publication:
Answer: Thank you very much for your kind feedback on our work.

1. The authors stated that the control group received treatment as usual. They should provide details of this usual treatment and whether it varies between different patients. This is important so that we know why we comparing the intervention against.

Answer: Thank you very much for this valuable advice. We have elaborated on this point in the manu-script (p. 9, ll. 172-175).

2. The authors reported results of comparison between two sequences of treatment (psycho-therapy followed by physiotherapy vs physiotherapy followed by psychotherapy) in the intervention group. However, this is not mentioned under the methods section. Although it is described in the protocol, it is important to mention this under the methods section

Answer: Thank you very much for this valuable advice. We have revised this aspect in the manuscript to clarify this point (p. 12, ll. 244-245).

3. As this is a pilot feasibility trial, the authors should calculate the sample size for future trials and advise on what should be the primary outcomes.

Answer: Thank you very much for this valuable advice. We have added an additional section to the man-uscript pointing out the urgent need for a power calculation and providing guidance on how to create an adequate study design for future research (p. 10, ll. 191-198).

VERSION 2 – REVIEW

REVIEWER	Zadro, Joshua University of Sydney, Institute for Musculoskeletal Health, School of Public Health
REVIEW RETURNED	29-Sep-2021

GENERAL COMMENTS	I thank the authors for being very attentive to my comments and suggestions. I am happy with the revised manuscript and have no further suggestions.

REVIEWER	Horne, Andrew The University of Edinburgh MRC Centre for Reproductive Health
REVIEW RETURNED	01-Oct-2021

GENERAL COMMENTS	Thank you for responding to my comments. I am happy with the revised manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Mr. Joshua Zadro, University of Sydney

Comments to the Author:

I thank the authors for being very attentive to my comments and suggestions. I am happy with the revised manuscript and have no further suggestions.

Answer: Thank you once again for reviewing our manuscript and giving us constructive and valuable feedback, which helped to improve the manuscript.

Reviewer: 2

Dr. Andrew Horne, The University of Edinburgh MRC Centre for Reproductive Health

Comments to the Author:

Thank you for responding to my comments. I am happy with the revised manuscript.

Answer: Thank you once again for the kind feedback on our work. Your review comments lead to substantial improvement of the manuscript.